REMARKS

Upon entry of the present amendment, claims 58 and 59 are amended; claims 69 and 70 are added; claims 1-48 have been cancelled without predjudice or disclaimer. Accordingly, claims 49-52, 54-65, and 68-70 are pending. Each of the rejections is addressed below.

Support for the Amendment

Support for the new claims is found in claims 49, 50, and 51 and in Applicants' specification as originally filed. In particular, support for administration of an effective amount of a nucleic acid encoding VEGF and an effective amount of GM-CSF and/or SCF is found in Applicants' specification, for example, at Examples 9-12, pages 45-59, page 58, lines 18-19, and page 58, lines 13-16.

Claim Objections

The objection to claims 58 and 59 is overcome by the present amendment.

Rejection under 35 U.S.C. § 103(a)

The Office rejects claims 49-52, 54-65, and 68, which are directed to methods for inducing new blood vessel growth in myocardial tissue and improving cardiac function, under 35 U.S.C. § 103(a) as obvious over International Publication No. Isner et al., WO 97/14307 (hereinafter "Isner") in view of Hammond et al., U.S. Patent No. 5,880,090, (hereinafter "Hammond"), and U.S. Patent No. Dillman et al., 6,605,274 (hereinafter "Dillman"). For the reasons detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

Isner

The Examiner acknowledges that differences exist between the prior art and the claimed invention. In particular, the Examiner finds that Applicants' claimed invention differs from that of Isner because (i) Isner fails to teach methods for administering a combination of a nucleic acid encoding an angiogenic protein and at least one angiogenic factor; and (ii) Isner further fails to teach methods for monitoring a cardiac function. At page 6, first paragraph, of the Office Action mailed on February 13, 2007, the Examiner states, "Isner does not teach that an angiogenic factor

can be combined with other genes or their encoded gene products to enhance the activity of targeted cells. Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches . . ." Accordingly, the Examiner has found that Isner alone is not sufficient to make the claimed invention obvious.

Dillmann

To remedy the alleged deficiencies of Isner, the Examiner cites Dillmann and Hammond. Dillmann provides a general description of methods for monitoring cardiac function. Dillmann fails to teach or suggest methods for administering a combination of a nucleic acid encoding an angiogenic protein and at least one angiogenic factor and subsequently monitoring a cardiac function. Dillmann fails entirely to teach or suggest modifying the methods described by Isner to arrive at Applicants' claimed invention. Such a teaching or suggestion is required in order to establish a prima facie case of obviousness. *In re Dembiczak*, 175 F.3d 994, 50 USPQ 2d 1614 (Fed. Circ. 1999). The Federal Circuit requires the Examiner to show some motivation to combine the references that establish obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). It is not sufficient to show that Applicants' claimed combination *could* be made. Rather, the Examiner must show some particular teaching or suggestion within the references themselves that the combination *should* be made.

Hammond

The Examiner relies on Hammond to remedy the deficiencies of Dillmann and the alleged deficiencies of Isner. Hammond describes methods for increasing **endothelialization** within a synthetic graft using cytokines. Hammond, like Dillman, fails to teach or suggest administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into myocardial tissue; administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, **inducing new blood vessel** growth in a myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells (EPC) in the mammal; and **monitoring a cardiac function** by echocardiography, ventricular end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), fractional shortening (FS), wall

motion score index (WMSI), electromechanical mapping, cardiac angiography or LV systolic pressure (LVSP).

Hammond merely describes methods to increase the number of endothelial cells that **attach to and coat the surface of a synthetic graft** (column 1, line 60, to column 2, line 5). In contrast, Applicants claims are directed to **inducing new blood vessel growth** in the myocardial tissue of a mammal. Induction of blood vessel growth is a multifaceted biological process that is clearly different from methods Hammond describes for coating a graft surface (column 2, lines 64-67.) One skilled in the art would lack the requisite expectation of success to employ cytokines that increase endothelialization in a synthetic graft as described by Hammond to induce the growth of new blood vessels as recited in Applicants' claims. The Examiner, citing Hammond, column 3, lines 28-37, alleges that Hammond describes the use of $CD34^+$ cells for the repair of ischemic tissue . Applicants respectfully disagree. In the cited passage, Hammond states that $CD34^+$ cell populations derived from peripheral blood "include a subset of cells that are capable in culture of differentiating into endothelial-like cells." (Hammond, column 3, lines 28-37). Hammond further states that it was "**proposed** that these circulating $CD34^+$ or $Flk\text{-}1^+$ cells participate in the repair of ischemic tissue." The cited passage fails to teach or suggest employing an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby **inducing the new blood vessel** growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells (EPC) in the mammal; and **monitoring a cardiac function.**

Asahara

The Examiner rejects claims 50, 51, and 57 under 35 U.S.C. § 103(a) over Isner, Hammond, Dillman and Asahara et al., (EMBO J. 18:3964-3972, 1999; hereinafter "Asahara"). Asahara teaches that "VEGF-induced mobilization of bone marrow-derived EPCs resulted in increased differentiated EPCs *in vitro* and augmented corneal neovascularization *in vivo*." Asahara describes the use of VEGF to induce the mobilization of bone marrow-derived EPCs. Asahara failed to appreciate, as Applicants' did, that the **combination** of a nucleic acid encoding

at least one angiogenic protein and at least one angiogenic factor, enhances the induction of blood vessel growth in a myocardial tissue. Asahara plainly teaches that VEGF is sufficient to induce vasculogenesis. To the extent that Asahara directs the skilled artisan towards the use of VEGF to induce vasculogenesis, he teaches away from Applicants' claimed invention, which recites administering to a mammal an effective amount of VEGF **and** a nucleic acid encoding at least one angiogenic protein. Thus, Asahara also fails to teach or suggest Applicants' claimed invention.

In sum, none of the cited references, alone or in any combination teaches or suggests a method for inducing new blood vessel growth in a myocardial tissue of a mammal by administering an effective amount of a nucleic acid encoding at least one angiogenic protein, administering an effective amount of at least one angiogenic factor, and monitoring a cardiac function as recited in Applicants' claims. Applicants were the first to appreciate that blood vessel growth could be induced using such methods, and that the growth of such blood vessels would improve cardiac function. It is not sufficient that one **could** have made the combination, the cited references must suggest the desirability of making the claimed combination and must further indicate that **the combination if made would have succeeded**. None of the references cited by the Office, alone or in any combination, teaches or suggests Applicants' claimed invention. The Office has failed to establish a *prima facie* case of obviousness. Thus, the rejection of the claims under U.S.C. § 103(a) should be withdrawn.

Double Patenting

Applicants acknowledge that claims 49-52, 54-65, and 68 are provisionally rejected over copending U.S. application No. 10/714,574. With regard to the provisional double patenting rejection over copending application No. 10/714,574, Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double-patenting rejection will be the only rejection remaining in the instant application. Therefore, pursuant to M.P.E.P. § 822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

Claims 69 and 70

New claims 69 and 70 have been added. Claims 69 and 70 are directed to methods for inducing new blood vessel growth in a myocardial tissue of a mammal by administering an effective amount of a nucleic acid encoding VEGF and GM-CSF and/or SCF. Applicants show that the combination of VEGF expression and GM-CSF and/or SCF administration is unexpectedly effective in inducing new blood vessel growth and improving cardiac function in myocardial tissue *in vivo* as shown in Examples 9-12, pages 45-59. In particular, Applicants describe a synergistic effect of this combination therapy *in vivo* experiments in swine and mouse models of chronic myocardial ischemia and acute myocardial infarction.

Applicants show a synergistic effect of G-CSF and SCF when administered in combination with VEGF-2 gene transfer in both acute myocardial infarction and chronic myocardial ischemia. Applicants state:

> More specifically, synergistic effect of cytokines (G-CSF+SCF) and VEGF-2 gene transfer was examined in acute and chronic myocardial ischemia (MI) . . . VEGF-2 GT was effective in acute and chronic MI. Therapeutic potential of the **combination therapy overwhelmed either sole treatment**. Histological examination using mice heart sections 1 week after acute MI/5 weeks after bone marrow (BM) transplantation revealed abundant recruitment of BM cells into ischemic myocardium in mice receiving the combination therapy. **These findings show clinical usefulness of the combination therapy**, especially in patients who are refractory to the sole treatment. (page 58, lines 18-26; emphasis added).

Not only was the combination of G-CSF and SCF with VEGF-2 gene transfer effective in recruiting endothelial progenitor cells (EPC), it was also effective in increasing vascularization in ischemic cardiac tissue under chronic and acute conditions (Figure 9A and 9B). Applicants state:

> For instance, in the swine study, selective left coronary angiography was performed to evaluate collateral development before and after treatment . . . These data indicated that **there was anatomic evidence of improved collateral formation in the Combo therapy group** compared with all other treatment groups. (page 54, line 23, to page 55, line 9; emphasis added).

In addition, Applicants found that VEGF-2 gene transfer when administered in combination with G-CSF and SCF increased microvascular capillary density when compared with either therapy

alone (page 55, lines 16-25). Therapeutic efficacy of the combination was not limited to increased blood vessel growth. VEGF expression in combination with G-CSF and SCF administration also synergistically increased cardiac function.

Applicants showed that the combination of VEGF-2 gene transfer, G-CSF and SCF treatment resulted in improved cardiac function in swine and mouse models of acute and chronic myocardial ischemia (Figure 11A-11C; page 56, line 16, to page 57, line 15). In particular, Applicants state that a "combination of cytokine treatment and VEGF-2 gene transfer improves LV [left ventricle] function in acute and chronic myocardial ischemia (page 56, lines 6-8)." Improved cardiac function was observed in both mice and swine. Applicants state:

> Accordingly, in chronic MI, **combo therapy resulted in superior improvement in all indices of perfusion and function** compared to all other treatment groups. **In both mice and swine, changes in echocardiographic fractional shortening and regional wall motion score were best in Combo therapy group** compared to other treatment groups. (Page 58, lines 4-7; emphasis added).

None of the cited references teach or suggest methods for inducing new blood vessel growth in a myocardial tissue of a mammal by administering an effective amount of a nucleic acid encoding VEGF in combination with GM-CSF and/or SCF. Importantly, none of the cited references, alone or in any combination, teach or suggest that the combination of VEGF expression and GM-CSF and/or SCF therapy would have a synergistic effect on new blood vessel growth and would improve cardiac function. Thus, new claims 69 and 70 are free and clear of the cited prior art. Allowance of the new claims is respectfully requested.

CONCLUSION

In view of the above amendment and Remarks, Applicants believe the pending application is in condition for allowance. If the Examiner disagrees, Applicants respectfully request that the Examiner contact the undersigned agent by telephone to schedule an interview prior to the mailing of an Office action.

Applicants believe that no fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

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Respectfully submitted,

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